DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
New England District

One Montvale Avenue
Stoneham, Massachusetts 02180
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WARNING LETTER

NWE-02-09W

VIA CERTIFIED MAIL

November 20, 2008

Mr. Patrick Brandon, Managing Partner
Dr. Richard Deslauriers, Partner
Contract Medical Manufacturing
1 Jacks Hill Road
Unit 3F
Oxford, CT 06478-1190

Dear Mr. Brandon and Dr. Deslauriers:

During an inspection of your firm, Contract Medical Manufacturing (CCM), 1 Jacks Hill Road, Oxford, CT, on September 10 through September 25, 2008, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures medical devices, specifically sterile Custom Cranial Implants (SCCI's) for (b) (4) (b) (4) Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. § 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulations found at Title 21, Code of Federal Regulations (C.F.R.), Part 820. We received undated responses from CMM and (b) (4) on October 28, 2008 (collectively referred to as "the response") concerning our investigator's observations noted on the Form FDA 483, List of Inspectional Observations that was issued to you. We address this response below, in relation to each of the noted violations. These violations include, but are not limited to the following:

1. Failure to ensure that when the results of a process cannot be fully verified by subsequent inspection and test, that the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results shall be documented, as required by 21 C.F.R. § 820.75(a). For example,

    - We did not observe any documentation to demonstrate that your packaging process for sterile Custom Cranial Implants, using your own package sealer has been validated by your personnel.
    - We did not observe any documentation to demonstrate that the ETO sterilization process performed at your facility utilizing your equipment, including two separate (b) (4) sterilization chambers, has been validated at your facility by your personnel.

Your response confirmed that a "stop shipment" was implemented on September 16, 2008 and is still in effect for all sterile custom cranial implants manufactured at CMM. We also acknowledge that (b) (4) will be initiating a recall of all sterile custom cranial implants manufactured by CMM.

Your response also indicated that validation operations will be initiated for the sterilization operations being conducted at CMM. Once these actions have been completed, we look forward to reviewing the completed documentation in response to this Warning Letter. We also note that your responses did not address FDA 483 item 2 regarding the seal integrity process. Please provide copies of validation reports of all operations when completed.

We also understand the (b) (4) We anticipate that this (b) (4) will clearly define the Quality System regulations that are required as a finished device manufacturer.

2. Failure to establish and maintain procedures for monitoring and control of process parameters for standard processes to ensure that the specified requirements continue to be met, as required by 21 C.F.R. § 820.75(b). Your firm did not present any procedures for the monitoring and control of process parameters used during ETO sterilization and packaging of your finished devices. For example, during the inspection we observed that your firm was recording the relative humidity (RH) in the processing room and not the RH in the sterilization chamber. We also observed that your firm was not maintaining or reviewing the temperature recorder charts generated during your sterilization process of sterile cranial implants.

Your response to this observation is inadequate. It indicates that procedures have been already updated. Your firm first needs to assure that validation is successful and then confirm that all the proper procedures are in place. Therefore, in your response to this Warning Letter, we look forward to reviewing your updated procedures, after completion of the successful validation, to reflect the validated methods.

3. Failure to maintain quality system records that include or refer to the location of procedures and the documentation of activities including records required by 21 C.F.R. § 820.20 and 820.40, as required by 21 C.F.R. § 820.186. For example, your firm has no documentation of the review and acceptance of sterilization validation activities conducted by (b) (4) on the sterile cranial implants you manufacture and distribute.

   During our inspection, we observed that (b) (4) provided CMM with results for the operational qualification and the performance qualification on two sterilization chambers, (b) (4) that are used by your firm to sterilize cranial implants. They also provided your firm results of accelerated aging studies performed on the sterilized cranial implants you distribute. There was no documentation that CMM personnel reviewed or accepted these above reports. On each of the three documents referenced above, there is a signature block marked, "Approval for Contract Medical Manufacturing (b) (4) Contract Medical Manufacturing". During our inspection we observed that (b) (4) representatives have signed off on these documents instead of CMM personnel. We also reviewed the (b) (4) (b) (4) The Quality Plan (schedule B) included in this (b) (4) lists CMM as being responsible for manufacturing and/or assembly process that delivers said products packaged and sterilized within specified tolerances and quality, including responsibility for process validation documentation.

We have reviewed your response and have concluded that it is inadequate because it does not address how CMM plans on overseeing your quality system responsibilities.

For example, in your response to item 1, (page 2 of 23), you indicated that (b) (4) approved the validation protocol on May 31, 2007. There is no documentation that CMM is reviewing and approving these significant manufacturing steps at your facility. As a finished device manufacturer, you are responsible for assuring that every device shipped from your facility meets all of the required specifications. It is not clear from your response that a specific unit is responsible for this important function. In your response to this Warning Letter, you need to provide a commitment that CMM is taking the appropriate steps to assure that a quality organization exists to at your medical device manufacturing facility and is capable of ensuring that the quality policy is understood, implemented and maintained at all levels of your organization.

We understand the (b) (4) We anticipate that this (b) (4) will clearly define your responsibilities as a finished device manufacturer.

4. Failure to establish and maintain adequate procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria and finished devices shall not be released for distribution until: (1) the activities required in the Device Master Record (DMR) are completed; (2) the associated data and documentation is reviewed; (3) the release is authorized by the signature of a designated

individual(s); and (4) the authorization is dated, as required by 21 C.F.R. § 820.80(d). At least seven (7) device history records reviewed during the inspection, had erroneous sterility results documented. All 7 lots of implants were released and distributed without any documentation that these results met your required acceptance criteria. For example:

- Cranial implant CI#12692, sterilization lot # 270030 was sterilized on 11/20/07. The DHR for this implant indicated that the product's sterilization start time was 5:57 pm on 11/20/07 and the sterilization end time was 3:30 pm 11/20/07. The required sterilization time is (b) (4) Also, the biological indicator (BI) results at the 24 and 48 hour timeframe were also recorded as "Y" which indicates a "yellow" or positive sterility result. The DHR was signed off on 11/26/07 and the product was shipped on 11/26/07.

- Cranial implant CI#12634 was sterilized on 11/9-10/07. The DHR for this implant indicated that the BI results at the 24 and 48 hour timeframe were recorded as "Y" which indicates a "yellow" or positive sterility result. The DHR was signed off on 11/12/07 and the product was shipped on 11/12/07.

- Cranial implant CI#12619 was sterilized on 11/1-2/07. The DHR for this implant indicated that the BI results at the 24 and 48 hour timeframe were recorded as "Y" which indicates a "yellow" or positive sterility result. The DHR was signed off on 11/5/07 and the product was shipped on 11/5/07.

- Cranial implant CI#12611 was sterilized on 11/1-2/07. The DHR for this implant indicated that the BI results at the 24 and 48 hour timeframe were recorded as "Y" which indicates a "yellow" or positive sterility result. The DHR was signed off on 11/2/07 and the product was shipped on 11/5/07.

- Cranial implant CI#12636 was sterilized on 11/9-10/07. The DHR for this implant indicated that the BI results at the 24 and 48 hour timeframe were recorded as "Y" which indicates a "yellow" or positive sterility result. The DHR was signed off on 11/12/07 and the product was shipped on 11/13/07.

- Cranial implant CI#12595 was manufactured and released on 10/28/08. The DHR was initially signed off on 10/25/07 and the implant was shipped on 10/25/07. However, this implant was returned to CMM for sterilization. The sterilization record, included in the DHR for this implant shows that the implant was sterilized on 11/5-6/07 and the BI results at the 24 and 48 hour timeframe were recorded as "Y" which indicates a "yellow" or positive sterility result. The sterilization record was signed off on 11/8/07 and the product was shipped out again on 11/8/07. The DHR did not include a documented final QC review for this sterilized implant and the label included with this DHR indicates the product was labeled as non-sterile.

- Cranial implant CI#12819 was sterilized on 1/7-8/08. The DHR for this implant indicated that the BI results at the 24 hour timeframe were recorded on top of each other, i.e., the result included both a "Y" and an "O" result. The letter "Y" indicates a "yellow" or positive sterility result and the letter "O" indicates an "orange" or negative sterility result. The DHR was signed off on 1/10/08 and the product was shipped on 1/14/08.

We note that our FDA-483 did not address this specific deficiency. Therefore, in your response to this Warning Letter, please provide your proposed corrective actions to prevent this violation from recurring.

5. Failure to establish and maintain procedures to ensure that device history records (DHR's) for each batch, lot or unit are maintained to demonstrate that the device is manufactured in accordance with the DHR, as required by 21 C.F.R. § Part 820.184. For example, your firm does not have any procedures to instruct employees on how to record sterilization data or interpret biological indicator test results.

As noted in item #2 above, your firm first needs to assure that validation is successful and then confirm that all the proper procedures are in place. Therefore, in your response to this Warning Letter, we look forward to reviewing your updated procedures, after completion of the successful validation, to reflect the validated methods.

6. Failure to review, evaluate and investigate any complaint involving the possible failure of a device, labeling or packaging to meet any of its specification, as required by 21 C.F.R. § 820.198(c). For example, your Complaint Processing Procedure, # 3852.1 does not assure that complete information is obtained in order to evaluate the event thoroughly. Step 3.2.3.1 of your SOP states that a reasonable effort should be made to obtain the details necessary to make a complaint investigation and that such efforts shall be made part of the file.

- Complaint, CMM# 2007.18, received on 11/13/07 noted a patient infection. There was no documentation in the complaint file to demonstrate that attempts were made to obtain additional information regarding the complaint. Your analysis / conclusion for this complaint indicated that "we have been given no information other than the fact that the patient has an infection." This complaint was still open on 9/25/08.

- Complaint, CMM# 2008.12.5, received on 5/23/08 noted the patient developed an infection after the first implant surgery. The file also notes that after the first implant was removed and a second implant was inserted, the patient developed another infection and a third surgery is noted as TBD (to be determined) in your file. Your records show that the complaint investigation was performed on 6/24/08. There was no documentation in the complaint file to demonstrate that attempts were made to obtain additional information regarding the complaint. Your analysis / conclusion for this complaint indicated that the implant was

shipped before CMM started performing sterilization and there was not sufficient evidence to take the investigation further. The complaint file was closed on 6/26/08.

- Complaint, CMM# 2008.28 received on 6/23/08 noted the patient developed an infection after surgery. This complaint represents the second event reported to the firm for the patient involved in CMM #2008.12.5, above This file did not include any documentation regarding patient identification, or possible failure of the device. The complaint file was closed on 7/31/08.

We acknowledge the changes being made to your current procedures. Your response appears to be adequate. However, we also understand that the (b) (4) [redacted] (b) (4) [redacted] *Based on any modifications to this document, you may need to revisit these procedures again. Please forward us copies of your revised complaint SOP's after all corrections have bee reviewed and approved by your quality system.*

7. Failure to promptly review evaluate and investigate any complaint that represents an event which must be reported to FDA under 21 C.F.R. part 806, as required by 21 C.F.R § 820.198(d). For example, during the inspection, your firm did not have any documentation available to demonstrate that the above 3 complaints were reviewed for MDR reportability. Step 3.3.3 of your complaint procedure, #3852.1 , states that each complaint will be evaluated as to whether or not the event must be reported to the FDA as a MDR.

   Also, on 9/13/08, your firm provided us with 4 reports of MDR's that were related to your cranial implants, MDR # 8010177-2008-00001 dated 11/26/07, MDR # 8010177-2008-00040 dated 8/19/08, MDR # 8010177-2008-00041 dated 5/20/08 and MDR #8010177-2008-00071 dated 11/7/07. Your firm had no record of the complaints associated with these MDR's nor was there any documentation to demonstrate that an investigation was performed for these events. At the conclusion of the inspection on 9/25/08, no further information was made available for these events.

We note that the FDA- 483 did not address this specific violation. Therefore, in your response to this Warning Letter, please provide your plan on how you will prevent this violation from recurring.

8. Failure to control labeling operations to prevent labeling mix-ups and to document the labeling used in the DHR, as required by 21 C.F.R. § 820.120(d). For example, cranial implant CI#12595 was manufactured and released on 10/28/08 with labeling that indicated the device was non-sterile. However, this implant was returned to CMM for sterilization and the sterilization record found in the DHR for this implant shows that the implant was sterilized on 11/5-6/07. The sterilization record was signed off on 11/8/07 and the product was shipped on 11/18/07. The only label included with this DHR indicates the product was labeled as non-sterile.

We acknowledge the changes being made to your current packaging and labeling operations. Your response appears to be adequate. Please forward us copies of your revised labeling SOP's after all corrections have been reviewed and approved by your quality system.

9. Failure to establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities, and to document such training, as required by 21 C.F.R. § 820.25(b). For example, training records lacked documentation that employees involved in the processing and sterilization of cranial implants received instruction in how to interpret test results and production data.

Your response indicates that you have already trained your personnel on revised procedures. This response appears to be inadequate. Based on the numerous corrective actions that will need to occur at your facility in response to this Warning Letter, you may need to revisit your personnel training program. Therefore, in your response to this Warning Letter, please provide your plan on how you will prevent this violation from recurring.

You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the FDA without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

We acknowledge the receipt of your letter dated October 14, 2008, indicating that you were planning on responding to the Form FDA-483 that was issued to your facility on September 25, 2008. We also acknowledge your email dated September 22, 2008, stating that a shipping hold was placed on all custom cranial implants until further notice.

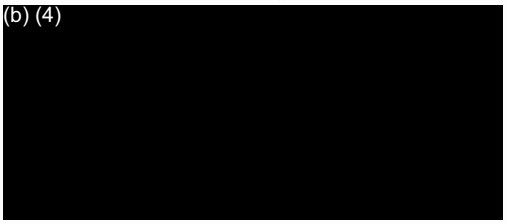
Your response should be sent to: Karen Archdeacon, Compliance Officer, Food and Drug Administration, One Montvale Avenue, 4th Floor, Stoneham, Massachusetts 02180. If you have any questions about the content of this letter please contact: Karen Archdeacon at (781) 596-7707.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. The specific violations noted in this letter and in the Inspectional Observations, Form FDA 483, issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely yours,

Anne Reid
Acting District Director
New England District

(b) (4)



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